Nucleophilic Substitution of Secondary Alkyl-Substituted Propargyl Acetates: An Economic and Practical Indium Trichloride Catalyzed Access

Min Lin, Lu Hao, Xiao-tao Liu, Qing-zhen Chen, Feng Wu, Ping Yan, Su-xia Xu, Xin-liang Chen, Jia-jie Wen, Zhuang-ping Zhan*

Department of Chemistry, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, Fujian, P. R. of China
Fax +86(592)2180318; E-mail: zpzhan@xmu.edu.cn

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Abstract: An economic and practical transformation from secondary alkyl-substituted propargyl acetates to a variety of nucleophilic substitution products was described. This reaction was catalyzed by inexpensive $InCl_3$. High yields and excellent chemoselectivity were obtained. The five-, six-, and seven-membered propargyl cycloethers were also successfully constructed by this protocol.

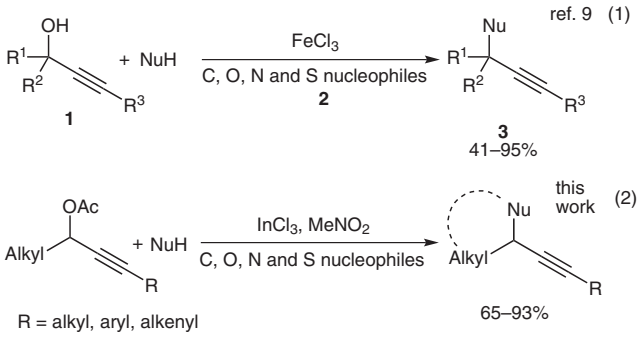
Key words: propargyl acetate, nucleophilic substitution, indium, propargyl cycloether

The Lewis acid catalyzed propargyl nucleophilic substitution has turned into an important organic transformation, as it provides a reliable and direct approach to a variety of propargyl products.[1] As a consequence, considerable attention has been paid to develop efficient conditions for it over the past decade. However, since the propargyl cation is generally less stable than its allyl analogue,[2] the vast majority of studies are limited to the employment of substrates possessing strong cation-stabilizing groups in the propargyl position: aryls or dialkyls in almost all cases;[3] and dicobalt complexes in the well-known Nicholas reaction.[4] Examples of nucleophilic substitution of secondary alkyl-substituted propargyl substrates remain very limited.

Recently, Gevorgyan et al. described an efficient $B(C_6F_5)_3$-catalyzed allylation of secondary alkyl-substituted propargyl acetates with allylsilanes.[5] This pioneer method allowed for the facile synthesis of 1,5-enynes in good to high yields with excellent functionality tolerance. Subsequently, in 2008, Brabander and co-workers demonstrated a Pt(II)-catalyzed intramolecular cycloetherification of secondary alkyl-substituted propargyl alcohol derivatives.[6] Also, Yoshimatsu et al. reported a $Sc(OTf)_3$-catalyzed substitution reaction of the phenylsulfanyl and phenylselanyl propargyl alcohols.[7] Despite the advantages of those works, the high price of catalysts or the narrow substrate scope was somewhat problematic, preventing their practical and large-scale utilization. Very recently, a cost-effective $InCl_3$-catalyzed three-component coupling of aldehydes, alkynes, and amines (A^3 coupling) producing propargyl amines via C–H activation was reported by Wang and co-workers.[8] Nevertheless, Wang's method was limited to the construction of C–N bond. Accordingly, development of more economic, practical as well as general catalytic system for the substitution reaction of secondary alkyl-substituted propargyl derivatives was highly desired.

Our recently reported iron(III) catalytic system provides an economic, practical, and efficient access to obtaining propargyl derivatives. Propargyl alcohols **1** undergo smooth conversion to the substitution products **3** but are mainly limited to aryl- or tertiary alkyl-substituted propargyl alcohols (Scheme 1, equation 1).[9] This method would be of even greater appeal if it was applicable to secondary alkyl-substituted propargyl systems, broadening the scope of propargyl substrates. Thus, as a result of the exploration in our group,[10] herein we report the inter- and intramolecualr nucleophilic substitution reaction of secondary alkyl-substituted propargyl acetates with a wide range of nucleophiles (Scheme 1, equation 2).

Initial attempt on the $FeCl_3$-catalyzed reaction between readily available **4** and ethanol in MeCN failed (Table 1, entry 1). On the basis of literature reports, the transformation undergoes an ionization (S_N1) mechanism: a propargyl cation intermediate was generated in the reaction mixture prior to substitution. Thus, solvent effect came into play as a dominant factor of stabilizing the propargyl cation during charge separation of the transition state. To test our hypothesis, we replaced MeCN with $MeNO_2$ as the solvent, which was generally considered stabilizing carbocations more efficaciously but coordinating with Lewis acid catalysts more weakly.



Scheme 1 Formation of propargyl derivatives by metallic Lewis acid catalyzed nucleophilic substitution reactions

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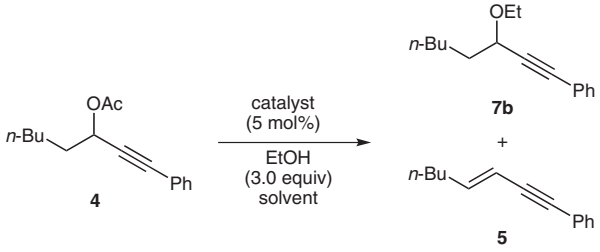
Table 1 Initial Results and Catalyst Optimization[a]

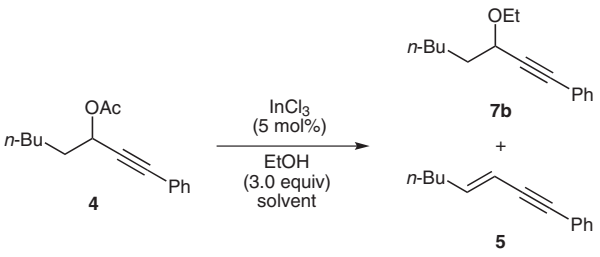


Entry	Catalyst	Reaction conditions	Yield (%)[b]	
			7b	**5**
1	$FeCl_3$	MeCN, 70 °C, 10 h	0	0
2	$FeCl_3$	$MeNO_2$, 70 °C, 20 min	49	41
3	$BiCl_3$	$MeNO_2$, 70 °C, 5 h	58	25
4	$ZnCl_2$	$MeNO_2$, 70 °C, 10 h	59	12
5	$AlCl_3$	$MeNO_2$, 70 °C, 20 min	53	37
6	$InCl_3$	$MeNO_2$, 70 °C, 20 min	86	0
7	$RuCl_3 \cdot 3H_2O$	$MeNO_2$, reflux, 12 h	0	0
8	$Cu(OTf)_2$	$MeNO_2$, 70 °C, 1 h	60	19
9	$Zn(OTf)_2$	$MeNO_2$, reflux, 12 h	0	0
10	AgOTf	$MeNO_2$, reflux, 12 h	18	0
11	$Bi(OTf)_3$	$MeNO_2$, 70 °C, 20 min	67	26
12	TMSOTf	$MeNO_2$, 80 °C, 4 h	61	24
13	$BF_3 \cdot OEt_2$	$MeNO_2$, 80 °C, 4 h	43	26
14	CF_3COOH	$MeNO_2$, reflux, 10 h	0	0
15	MeCOOH	$MeNO_2$, reflux, 10 h	0	0

[a] All reactions were carried out on a 1 mmol scale using 5 mol% of catalyst, 3 equiv of EtOH at appropriate temperature.
[b] Isolated yields.

Gratifyingly, the use of $MeNO_2$ at 70 °C substantially improved the reaction outcome (49%; Table 1, entry 2), but with poor chemoselectivity (41% of elimination product **5**). Then, we scanned a variety of Lewis acids for the most effective catalyst (Table 1). The screening results disclosed the $InCl_3$ to be more efficient than any other catalyst (86%; Table 1, entry 6). Neutral and covalent Lewis acids such as $AlCl_3$ and BF_3 gave similar yields and chemoselectivity as $FeCl_3$ did (Table 1, entries 5 and 13). Brønsted acids, including trifluoroacetic acid and acetic acid had no effect on this substitution (Table 1, entries 14 and 15). Trifluoromethanesulfonate salts, such as $Cu(OTf)_2$, $Zn(OTf)_2$, AgOTf, and $Bi(OTf)_3$, were considered having stronger Lewis acidity and better catalytic activity than corresponding halogen analogues by virtue of the very strong electron-withdrawing property of trifluoromethanesulfonate anion. However, these catalysts showed very different results, among which only $Cu(OTf)_2$ and $Bi(OTf)_3$ afforded the desired product as well as the elimination product in moderate yields (Table 1, entries 8 and 11). On the basis of the results shown above, we chose $InCl_3$ as the catalyst for this propargyl substitution.

Table 2 Screening of Reaction Solvents[a]



Entry	Solvent	Reactions conditions	Yield (%)[b]	
			7b	**5**
1	MeCN	reflux, 24 h	0	36
2	DMF	reflux, 24 h	0	0
3	DMSO	reflux, 24 h	0	0
4	CH_2Cl_2	reflux, 10 h	67	0
5	DCE	reflux, 3 h	75	0
6	1,4-dioxane	reflux, 10 h	0	0

[a] All reactions were carried out on a 0.5 mmol scale using 5 mol% of $InCl_3$, 3 equiv of EtOH under reflux conditions.
[b] Isolated yields.

The next solvent search demonstrated that replacement of $MeNO_2$ with less polar MeCN afforded only elimination product (36%; Table 2, entry 1). Conversely, the more polar DMF and DMSO resulted in neither desired product **7b** nor elimination product **5** (Table 2; entries 2 and 3). It was reasoned the catalytic activity of $InCl_3$ was dramatically suppressed by the strong coordination of DMF or DMSO with the metal, although the cation-stabilizing ability of $MeNO_2$ was not efficient as those of DMF and DMSO. Dichloromethane and 1,2-dicholoroethane exhibited a similar chemoselectivity as $MeNO_2$ despite lower yields (67% and 75%, respectively; Table 2, entries 4 and 5). 1,4-Dioxane did not give any product (Table 2, entry 6).

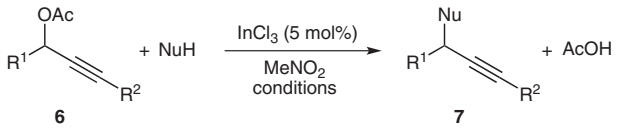
Examination of catalysts and solvents indicated that the combination of $InCl_3$ and $MeNO_2$ was a reasonably efficient catalytic system for the nucleophilic substitution of secondary alkyl-substituted propargyl acetates. Importantly, compared with other combinations, no elimination product was obtained, and higher yield was achieved.

Next, the generality of this nucleophilic transformation was examined. We were pleased to find this transformation to be very general for a wide range of propargyl acetates and nucleophiles (Table 3). Importantly, the reaction proceeded smoothly without exclusion of moisture and air. High yields and selectivity were observed in most cases examined. Alkyne parts, bearing phenyl (Table 3, entries 1–15), alkyl (Table 3, entries 16–19), and alkenyl

(Table 3, entries 20–24) substituents, underwent smooth conversions upon treatment with a series of nucleophiles. Primary and secondary alkyl alcohols, propargyl and benzyl alcohols reacted well to furnish the propargyl ethers in 69–87% yields within one hour.

The terminal triple bond and bromo functionalities were perfectly tolerated under the reaction conditions (Table 3, entries 11, 19, and 22). Carbon nucleophiles, such as allyltrimethylsilane, showed higher reactivity and required milder reaction conditions (Table 3, entries 1, 8, and 20). Interestingly, the ambident nucleophiles involving naphthalen-2-ol and phenol resulted in complete Friedel–Crafts arylated products **7g** and **7m** without any oxygen-substituted products observed (Table 3, entries 7 and 13). We also extended this protocol to heteroaromatic nucleophiles including furan. The α-substituted products **7n** and **7w** were given in good yields (Table 3, entries 14 and 23). Metallic Lewis acid catalyzed substitution of propargyl alcohols with thiols had been generally considered difficult to achieve, in large part because sulfur-containing compounds were catalyst poisoning caused by the strong coordination nature of sulfur atom. However, by using our method, the construction of sp^3 C–S bond was successfully fulfilled with several representative nucleophiles (Table 3, entries 3, 4, and 15). Propargylic acetate possessing an aryl substituent on the alkyne part reacted rapidly with benzenethiol affording the corresponding aryl sulfide ether **7c** in excellent yield with complete regioselectivity (Table 3, entry 3). Finally, selected amides also acted as an efficient nucleophile to provide the *N*-propargyl sulfonamides in excellent yields and a clean formation of two sulfonamides **7e** and **7q** were obtained in 92% and 91% yields, respectively (Table 3, entries 5 and 17). Unfortunately, the propargylation did not occur under these conditions when acetamides, anilnes, and piperidine were used as nucleophiles.

Table 3 $InCl_3$-Catalyzed Nucleophilic Substitution of Propargyl Acetates [a]



6 7

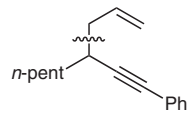
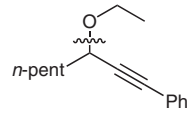
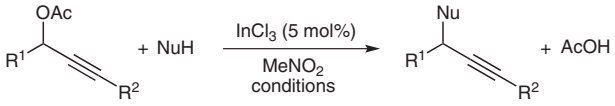
Entry	Product	Conditions	Yield (%)[b]
1[c]	 **7a**	r.t., 0.5 h	93
2	 **7b**	70 °C, 0.4 h	86

Table 3 $InCl_3$-Catalyzed Nucleophilic Substitution of Propargyl Acetates [a] (continued)



6 7

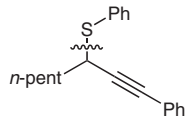
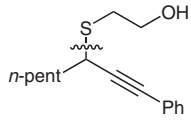
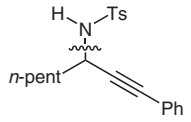
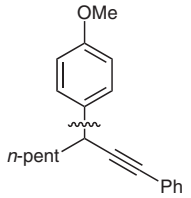
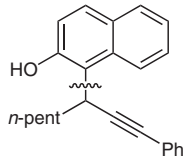
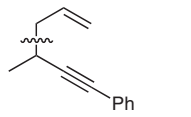
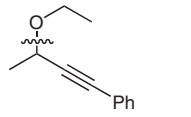
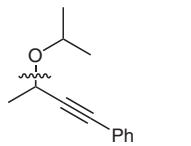
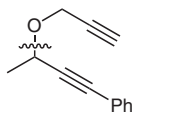
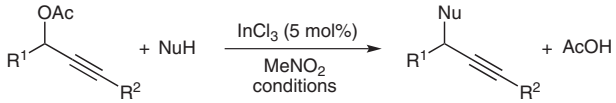
Entry	Product	Conditions	Yield (%)[b]
3	 **7c**	50 °C, 0.5 h	79
4	 **7d**	70 °C, 0.5 h	65
5	 **7e**	r.t., 0.5 h	92
6	 **7f**	35 °C, 0.4 h	88
7	 **7g**	50 °C, 0.5 h	86
8[c]	 **7h**	r.t., 0.5 h	91
9	 **7i**	70 °C, 0.5 h	84
10	 **7j**	70 °C, 1.0 h	69
11	 **7k**	70 °C, 0.5 h	87

Table 3 $InCl_3$-Catalyzed Nucleophilic Substitution of Propargyl Acetates [a] (continued)



6 **7**

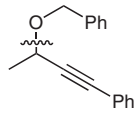
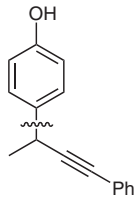
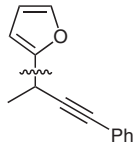
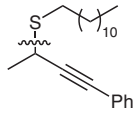
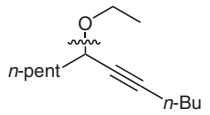
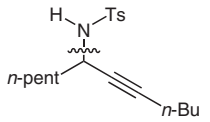
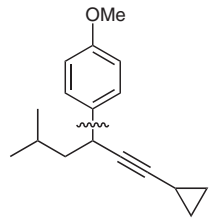
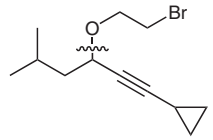
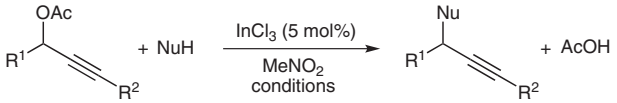
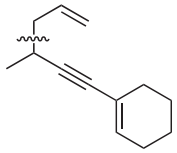
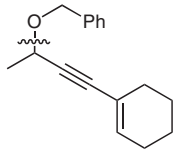
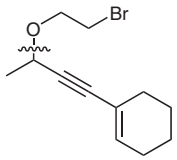
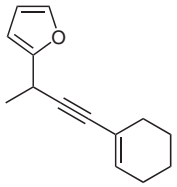
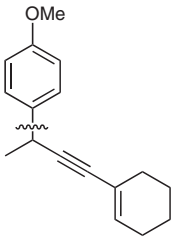
Entry	Product	Conditions	Yield (%)[b]
12	 **7l**	70 °C, 0.5 h	85
13	 **7m**	70 °C, 0.5 h	83
14	 **7n**	70 °C, 0.5 h	83
15	 **7o**	70 °C, 0.5 h	79
16	 **7p**	70 °C, 1.0 h	81
17	 **7q**	70 °C, 0.4 h	91
18	 **7r**	50 °C, 0.4 h	86
19	 **7s**	50 °C, 0.5 h	84

Table 3 $InCl_3$-Catalyzed Nucleophilic Substitution of Propargyl Acetates [a] (continued)



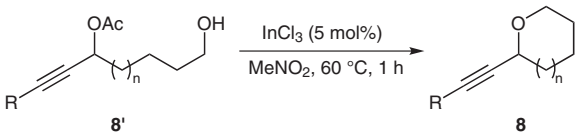
6 **7**

Entry	Product	Conditions	Yield (%)[b]
20[c]	 **7t**	r.t., 0.5 h	89
21	 **7u**	50 °C, 0.5 h	82
22	 **7v**	50 °C, 0.5 h	85
23	 **7w**	70 °C, 0.5 h	80
24	 **7x**	40 °C, 0.5 h	83

[a] Reaction conditions: propargyl acetate (0.5 mmol), nucleophile (1.5 mmol), $InCl_3$ (5 mol%), $MeNO_2$ (2.0 mL).
[b] Isolated yields based on propargyl acetates **6**.
[c] The allyltrimethylsilane was used as the nucleophile.

Propargyl cycloethers have received much attention in recent years, and many synthetic and natural propargyl cycloesters have displayed important biological activity or been used as synthetic precursors.[11] Although a number of methods are available for their synthesis, the development of general and efficient synthetic methodologies is still highly attractive. Thus, we investigated the efficacy of intramolecular cyclization toward five-, six-, and seven-membered propargyl cycloethers by this method (Table 4). To our delight, it was found that propargyl cycloethers could be synthesized in moderate to excellent

Table 4 Synthesis of Propargyl Cycloethers via $InCl_3$-Catalyzed Intramolecular Nucleophilic Substitution of Propargyl Acetates[a]



Product	R	n	Yield (%)[b]
8a	Ph	0	91
8b	Ph	1	89
8c	Ph	2	68
8d	cyclohex-1-en-1-yl	0	90
8e	cyclohex-1-en-1-yl	1	88

[a] Reaction conditions: propargyl acetate (1.0 mmol), $InCl_3$ (5 mol%), $MeNO_2$ (2.0 mL).
[b] Isolated yields.

yields under mild reaction conditions. As can be seen from Table 4, the yields of expected products from phenyl- or cyclohexenyl-substituted propargyl acetates are of slight difference in the formation of five- and six-membered propargyl cycloethers **8a**,**b**,**d**,**e**, while the yield of seven-membered product decrease dramatically, leading to a moderate yield of **8c**.[12,13]

In summary, we have developed an economic, general, and highly practical method for both intermolecular and intramolecular nucleophilic substitution of secondary alkyl-substituted propargyl acetates with a wide range of nucleophiles, which provides an expeditious and efficient route to various propargyl compounds. This work also represents a valuable complement to existing procedures for the synthesis of propargyl derivatives. Further studies to extend the scope of synthetic utility for this $InCl_3$-catalyzed substitution reaction are in progress in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **General Procedure A for the Intermolecular Substitution Reactions between Alkyl-Substituted Propargyl Acetates and Nucleophiles**

To a 5 mL flask were successively added propargyl acetate (0.5 mmol, 1.0 equiv), nucleophile (1.5 mmol, 3.0 equiv), $MeNO_2$ (2 mL) and anhyd $InCl_3$ (6 mg, 0.025 mmol) at r.t. Then, the mixture was magnetically stirred at appropriate temperature until the reaction was completed as monitored by TLC. The reaction mixture was cooled down to r.t., and the solvent was removed under reduced pressure. Then the residue was purified by flash chromatography on silica gel to afford the substitution product.

(13) **General Procedure B for the Intramolecular Substitution Reactions of Alkyl-Substituted Propargyl Acetates**

To a 5 mL flask were successively added propargyl acetate (1.0 mmol), $MeNO_2$ (2 mL) and anhyd $InCl_3$ (12 mg, 0.05 mmol) at r.t. Then, the mixture was magnetically stirred at 60 °C for 1 h. The reaction mixture was cooled down to r.t., and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the intramolecular substitution product.